Title: A comparative molecular surface analysis (COMSA) : a new efficient technique for drug design

Author: Jarosław Polański, Rafał Gieleciak, Andrzej Bąk, Krystyna Jarzembek, M. Wyszomirski

A COMPARATIVE MOLECULAR SURFACE ANALYSIS (COMSA). A NEW EFFICIENT TECHNIQUE FOR DRUG DESIGN

JAROSŁAW POLAŃSKI[1], RAFAŁ GIELECIAK[1], ANDRZEJ BĄK[1], KRYSTYNA JARZEMBEK[1] and MIROSŁAW WYSZOMIRSKI[2]

[1] Institute of Chemistry, University of Silesia, Katowice
[2] University of Bielsko-Biała, Bielsko-Biała

Abstract: Several applications of the COMSA were discussed including a series of the potential anti-HIV drugs and a series of dyes.

Keywords: COMSA, anti-HIV drugs.

Although it is usually believed that 3D methods offer a clear advantage over the traditional Hansch approach, the latter seems to keep safe. The results of classical 3D QSAR techniques, in particular COMFA, are very sensitive even to a minute changes in the alignment of molecules, which both complicate any study and bring a problem of chance correlation. On the other hand, standard 3D descriptors performed less successful than 2D fingerprints. These facts clearly indicate that new concepts and computational tools are still needed. One of the alternatives of the potential use in this field are neural networks, and particularly self–organizing neural networks, which can be applied to design much more flexible techniques.

The aim of the current work is to discuss the results of the study aimed at the implementation of the coupled neural network (self–organizing Kohonen map) and PLS system for analyzing the similarity of three dimensional molecular surfaces, modeling 3D QSARs and predicting molecular properties.

EXPERIMENTAL

All the data are extracted from the literature (1–5). For modeling purposes we used CORINA, PETRA, MATCH 3D, SURFACE and KMAP programs run on SGI workstation. Alternatively, we used MATLAB environment for programming the neuronal and PLS calculations. All the procedures are detailed elsewhere (4,5).

RESULTS AND DISCUSSION

A comparison of the Kohonen maps of the electrostatic potential can be used to illustrate and interprete the differences between molecules. It has been demonstrated before that even if we cannot explain molecular effects, the style of the maps often correlates with biological activity of the molecules. Although the method proved its usefulness, there are some complications. The dependence of the final pattern upon many parameters controlling the performance of neural network, and consequently the dependence upon the software used for simulation, seems to be one of the most important. In order to illustrate this problem we will use here an example of the organic peroxides of antimalarial activity. The Kohonen maps of these compounds were simulated by Jefford et al. and reported in Ref. (7). In Figure 1a to 1f we used different color scales (A, B) in order to obtain maximal similarity to the original maps (7), but, in fact, we failed to find satisfactory similarity.

In contrast, we have observed that the use of the so called comparative Kohonen mapping can provide highly reproducible results. Recently, we have designed the COMSA method capable of quantitative modelling of 3D QSARs. Table 1 compares the COMSA and COMFA models obtained for several series of bioactive compounds. The COMSA results are always at least slightly better than the COMFA ones.

Despite many efforts, SAR data cannot always be modeled to take the form of the quantitative QSAR. In such cases a comparative method can also be used for visualizing SAR data. We have shown recently that it can be used for a rapid screening of the activity of

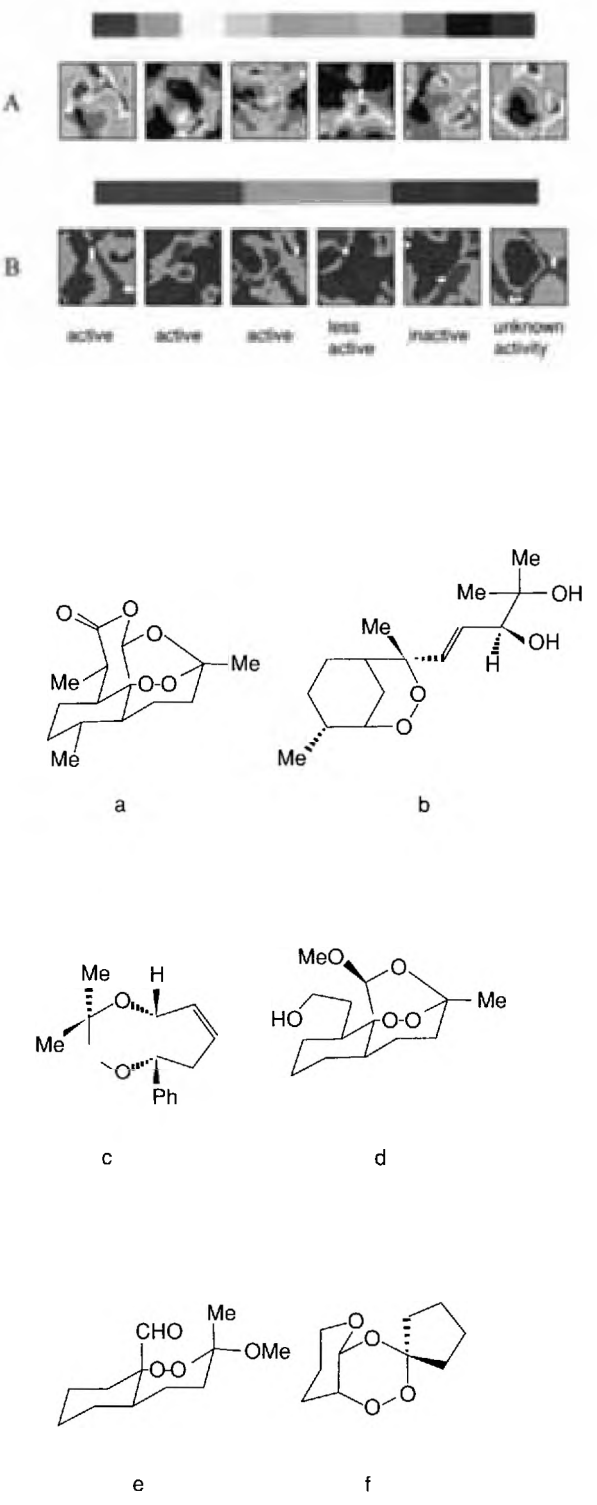

Figure 1. The Kohonen maps of some organic peroxides of antimalarial activity.

styrylquinolines – new inhibitors of HIV integrase (8). This method not only gave us a clear hint explaining the most important molecular feature controlling the activity of the series of novel HIV inhibitors, but also was predictive enough to give a proper guess for the activity of a set of newly synthesized compounds.

Table 1. A comparison of the COMSA and COMFA models obtained for several bioactive series.

Model	Compounds	Type of activity	COMSA q^2 (no. of components)	COMFA q^2 (no. of components)
1	Benzoic acids[a]	pK_a	0.90 (5)	0.75 (5)
2	Alkanoic acids[a]	pK_a	0.86 (5)	0.52 (5)
3	HEPT–inhibitors HIV–1 (RT)[b]	log(1/C)	0.79 (4)	0.73 (7)
4	Anthraquinone vat dyes[c]	affinity	0.88 (7)	0.84 (5)
5	Sulfinoquinolines[d]	$log(LD_{50})$	0.89 (8)	0.70 (6)
6	Steroids[e]	affinity	0.77 (5)	0.72 (5)
7	CBG[f]	affinity	0.88 (1)	0.73 (4)
8	TBG[f]	affinity	0.76 (5)	0.76 (8)
9	Benzoic acids[f]	Hammett constant	0.91 (4)	0.92 (8)

The data were taken from: [a] Ref. [4], [b] Ref. [6], [c] Ref. [2], [d] Ref [1], [e] Ref [3], [f] Ref. [5].

Using this technique we designed new synthetic targets which we are now synthesizing in our laboratory.

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REFERENCES

1. Boryczka S., Wietrzyk J., Opolski A.: Pharmazie 57, 151 (2002).
2. Fabian M.F.W., Timofei S., Kurunczi L.: J. Mol. Struct. (Theochem) 340, 73 (1995).
3. Beger D. R., Buzatu A.D., Wilkes G. J., Lay O. J.: J. Chem. Inf. Comp. Sci. 41, 1360 (2001).
4. Polański J., Gieleciak R., Bąk A.: J. Chem. Inf. Comput. Sci. 42, 184 (2002).
5. Polański J., Walczak B.: Comp. & Chem. 24, 615 (2000).
6. Hannongbua S., Lawtrakul L., Sotriffer A. Ch., Rode B.M: Quant. Struct. – Act. Relat. 15, 389 (1996).
7. Jefford W.C., Grigorov M., Weber J., Luthi H.P., Tronchet J.M.J.: J. Chem. Inf. Comput. Sci. 40, 354 (2000).
8. Polański J., Zouhiri F., Jeanson L., Desmaële D., d'Angelo J., Mouscadet J.–F., Gieleciak R., Gasteiger J., Le Bret M.: J. Med. Chem. *in print.*

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